Excitatory Amino Acid Metabotropic Receptor Subtypes and Calcium Regulation

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Calcium (Ca^{2+}) possesses a pivotal role in a large variety of cellular processes. In neurons, it represents an essential step in the mechanisms triggering synaptic plasticity, long-term potentiation,[1,2] long-term depression,[3–5] cytoskeletal organization,[6] exocytosis,[7,8] and delayed neurotoxicity.[9] Considering all these distinct fundamental roles of Ca^{2+}, one may logically suppose that they result from specific changes in intracellular Ca^{2+} concentration, which differ in their amplitude, duration, and location. All these subcellular Ca^{2+} variations should be tightly regulated to avoid the emergence of uncontrolled mechanisms, often leading ultimately to cell death. Many systems contribute to this regulation, namely, membrane sodium (Na^+)/Ca^{2+} exchangers, Ca^{2+} pumps (Ca^{2+}-ATPases), Ca^{2+} binding proteins, and Ca^{2+} channels. The later category could be divided into five main subtypes: voltage-dependent Ca^{2+} channels (VDCC), receptor-operated Ca^{2+} channels (ROC), G-protein-operated Ca^{2+} channel (GOC), second messenger-operated Ca^{2+} channels (SMOC), and finally Ca^{2+} release-activated channel (CRAC), as recently proposed[10] (FIG. 1). Glutamate (Glu), which is the main excitatory neurotransmitter in the brain, may directly or indirectly modulate most of the above-mentioned Ca^{2+} channels. Its action occurs via two main classes of receptors, namely, the ionotropic and the metabotropic receptors as shown in FIGURE 2. Ionotropic Glu receptors (iGluR) are composed of subunit proteins, which form an integral ligand-gated ion channel. iGluR can be subdivided into two main categories, the *N*-methyl-D-aspartate (NMDA) receptors and the non-NMDA ones. The NMDA receptor family are receptor-channels, permeable to Ca^{2+} (ROC). The non-NMDA receptors, composed of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors and kainic acid (KA) receptors, are also receptor-channels, generally almost impermeable to Ca^{2+}. The exception to this last statement is the existence of AMPA receptors lacking the GluR2 subunit, which are permeable to Ca^{2+}. The activation of the non-NMDA receptors produces a depolarization, which opens the VDCC. The second class of receptors, the metabotropic glutamate receptors (mGluR) are linked to G-proteins. Their stimulation generates the formation of second messengers and/or regulates ion channel function. Molecular cloning by cross-hybridization and polymerase chain reaction (PCR) has revealed the existence of at least seven subtypes of mGluR.[11–16] The mGluR can be subdivided into three main subgroups according to DNA sequence similarities, receptor-associated signal transduction, and the agonist selectivities[17] (FIG. 2). In agreement with their high sequence

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homology, both mGluR1 and mGluR5 stimulate the phosphoinositide metabolism, leading to IP3 synthesis and Ca^{2+} mobilization from the endoplasmic reticulum. The most potent agonist of these receptors is quisqualate (QA), as previously reported,[18] whereas *trans*-1-aminocyclopentane-1,3-dicarboxylic acid (*t*-ACPD) is a very weak agonist. These receptors also induce arachidonic acid release. The two other mGluR subgroups are composed of receptors coupled to the inhibition of forskolin-

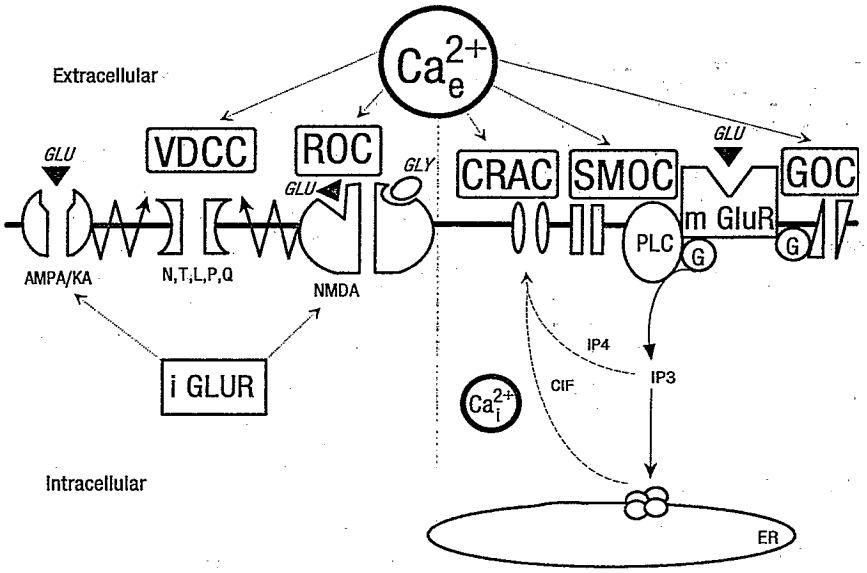

FIGURE 1. Schematic representation of possible mechanisms and pathways of Ca^{2+} influx by excitatory amino acid receptor activation. Ca^{2+} influx may occur through voltage-dependent Ca^{2+} channels (VDCC), receptor-operated Ca^{2+} channels (ROC), Ca^{2+}-release activated Ca^{2+} channels (CRAC), second messenger-operated Ca^{2+} channels (SMOC), and G-protein-operated Ca^{2+} channels (GOC). Ionotropic glutamate receptors (iGluR) are all able to activate VDCC, whereas only the *N*-methyl-D-aspartate (NMDA) is permeable to Ca^{2+} (ROC). The metabotropic glutamate receptor (mGluR) could be associated via a G-protein to GOC or could activate indirectly CRAC or SMOC. The SMOC activation may be due to the inositol-1,4,5-trisphosphate (IP3) synthesis from membrane inositol phospholipids, catalyzed by the phospholipase C enzymes (PLC), or inositol-1,3,4,5-tetrakisphosphate (IP4), or Ca^{2+}, or Ca^{2+} influx factor (CIF). CRAC may result from emptying the endoplasmic reticulum (ER) Ca^{2+} pool. Other abbreviations: Glu, glutamate; Gly, glycine; AMPA, RS-α-amino-3-hydroxy-5-methyl-4-isoxazole propionate; KA, kainate.

stimulated adenylate cyclase activity. Their discrimination arises from their agonist selectivity. mGluR2 and mGluR3 are potently activated by *t*-ACPD and Glu, whereas QA is almost ineffective. mGluR4, mGluR6, and mGluR7 are preferentially activated by 2-amino-4-phosphonobutyric acid (AP4), which is more potent than Glu by one order of magnitude. *t*-ACPD is a very weak agonist at these receptors, and QA presents almost no agonist activity.

Altogether, these facts indicate that Ca^{2+} represents a converging step for most,

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if not all, excitatory amino acid (EAA) receptor types. In turn, Ca^{2+} ions possess numerous targets: calmodulin, which activates Ca^{2+} calmodulin kinase; protein kinases C (PKC), which are translocated from the cytosol to the plasma membrane; phospholipase C; phospholipase A2; early genes; and channels. As feedback, all the stimulated targets may directly or indirectly regulate the activity of the EAA receptor subtypes. Indeed, EAA receptors themselves could serve as substrates for the various kinases, which modulate their respective activity by phosphorylation. For instance, PKC activation is known to enhance NMDA currents.[19] The phosphoryla-

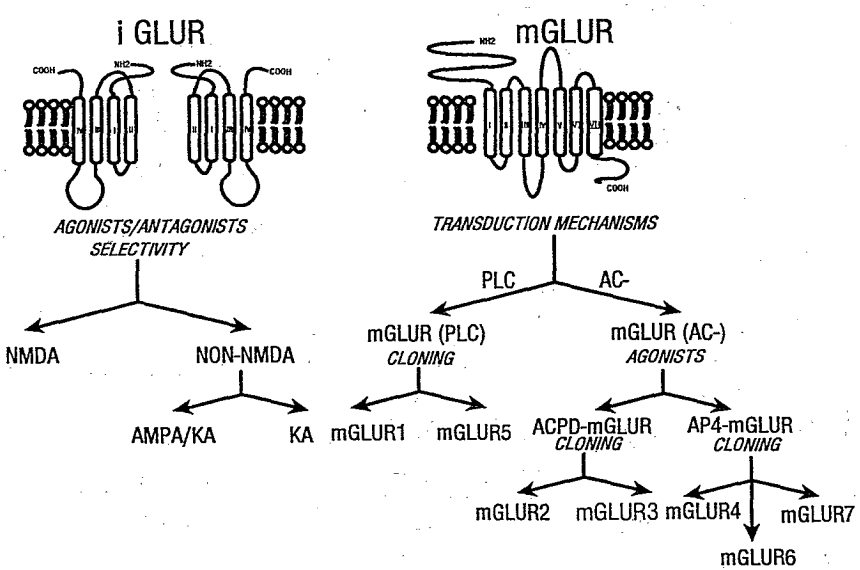

FIGURE 2. Classification of ionotropic glutamate receptors (iGluR) and metabotropic glutamate receptors (mGluR). iGluR are divided into *N*-methyl-D-aspartate (NMDA) and non-NMDA types according to their respective agonist and antagonist selectivity. The non-NMDA is further subdivided into AMPA (RS-α-amino-3-hydroxy-5-methyl-4-isoxazole propionate)/KA (kainate) and KA with respect to the agonist selectivity of these two substances. The mGluR are classified into two groups—those linked to the phospholipase C (PLC) enzymes, named mGluR (PLC), and those coupled to the inhibition of adenylate cyclase (AC-), named mGluR (AC-). This latter group is made up of two types, defined by the agonist selectivity of 2-amino-4-phosphonobutyrate (AP4) and *trans*-1-aminocyclopentane-1,3-dicarboxylate (ACPD). Finally, a last subdivision is obtained from receptor cloning, suggesting that up to seven receptor types exist.

tion of several distinct sites on the NR1 subunit of the NMDA receptor may be catalyzed by PKC.[20,21] Consequently, Ca^{2+} represents one of the main centers for the cross talk between most, if not all, EAA receptor subtypes. This concept could likely be extended to many other neurotransmitter receptors.

This paper, however, is restricted to the role of EAA metabotropic receptors linked to phospholipase C (PLC) in the regulation of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) during development and, reciprocally, on the modulation by Ca^{2+} of the EAA-stimulated inositol phosphate (IP) metabolite formation. The activation of

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PLC-linked receptors is known to induce the formation of two second messengers, namely, inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) from the cleavage of membrane inositol lipid, phosphatidylinositol 4,5-bisphosphate (PIP2).[22,23] Whereas DAG activates protein kinase C (for a review, see ref. 24), IP3 releases Ca^{2+} from intracellular organelles possessing IP3 receptors, such as the endoplasmic reticulum.[25] However, it became apparent that IP3-sensitive Ca^{2+} stores have a limited capacity and could not completely account for the substantial $[Ca^{2+}]_i$ increase, subsequent to EAA receptor activation. Moreover, it was reported that, in many cell types, receptor-mediated $[Ca^{2+}]_i$ augmentation invariably results from both a Ca^{2+} mobilization from intracellular stores and a Ca^{2+} influx from the extracellular medium.[26–32] The mechanism(s) as well as the molecular nature of the channel(s) that mediate IP3-induced Ca^{2+} influx remain unknown. Two main hypotheses have been proposed.[33] First, IP3 and/or inositol 1,3,4,5-tetrakisphosphate (IP4) directly gate a Ca^{2+} channel on the plasma membrane.[34] The other alternative, termed the capacitive Ca^{2+} entry hypothesis, is that emptying the intracellular Ca^{2+} stores by IP3 represents the triggering stimulus for Ca^{2+} entry (FIG. 1). This later hypothesis necessitates a communication between the endoplasmic reticulum, which represents the store to be emptied, and the plasma membrane, where the Ca^{2+} channel is located. The three possibilities proposed[33] for this communication are a diffusible messenger, a signal given by a low Ca^{2+} concentration near the plasma membrane, and protein-protein interaction (a direct interaction between IP3 receptors and Ca^{2+} channel, for instance). The first possibility is supported by the discovery of a soluble small molecule, named Ca^{2+} influx factor (CIF)[35] and by electrophysiological patch-clamp experiments.[36] The second possibility is far less substantiated although it has been demonstrated that decreasing cytosolic Ca^{2+} could increase Ca^{2+} entry.[37] The third proposal could be evidenced by the fact that intracellular Ca^{2+} increases the sensitivity of IP3 receptors, likely directly associated with the plasma membrane Ca^{2+} channel and to IP3, which may represent a Ca^{2+} sensor for evaluating the Ca^{2+} level of the store.[38,39] The involvement of G-proteins has also been proposed on the basis of whole-cell patch-clamp experiments showing that GTPγS, but not ALF_4^-, prevents the Ca^{2+} influx.

We report evidence indicating that, in nerve terminals, the intracellular Ca^{2+} release from IP3-sensitive stores following EAA metabotropic receptor activation directly or indirectly produces a depolarization, likely by opening a Ca^{2+}-activated nonspecific cation channel (CAN). Subsequently, the activation of this CAN channel leads to an extracellular Ca^{2+} influx through a new voltage-dependent, Mn^{2+} impermeable Ca^{2+} channel. This influx activates Ca^{2+}-sensitive PLC, which results in an increased IP3 production.

CALCIUM INCREASE MAINLY RESULTS FROM EXCITATORY AMINO ACID METABOTROPIC RECEPTOR ACTIVATION IN SYNAPTONEUROSOMES

We previously showed that all the classical antagonists of the iGluR, namely, D-2-amino-5-phosphonovalerate (APV), 6-nitro-7-cyanoquinoxaline-2,3 dion (CNQX), glutamate-aminomethyl-sulfonate, and γ-D-glutamylglycine neither affected the QA-, Glu- nor the *t*-ACPD-induced IP formation in 8-day-old rat forebrain synaptoneurosomes.[18,40] The agonists QA, *t*-ACPD, and Glu produce a dose-dependent increase in intracellular Ca^{2+} (reaching up to 70 nM) as measured by Fura-2 fluorescence. The pharmacology of this mGluR agonist-elicited Ca^{2+} increase is highly correlated with that reported for the stimulation of IP metabolism[41]

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(FIG. 3). Moreover, the iGluR antagonists did not block the QA-, Glu- or *t*-ACPD-induced Ca^{2+} increase.

Taken together these data strongly suggest that the intracellular Ca^{2+} rise in synaptoneurosomes essentially originates from mGluR activation.

ORIGIN OF Ca^{2+} PRODUCING THE INTRACELLULAR Ca^{2+} RISE

QA (10 μM) induces a long-lasting increase in intracellular Ca^{2+} of about 70 nM in the presence of an extracellular Ca^{2+} concentration ($[Ca^{2+}]_e$) of 150 μM. In the presence of 150 μM of the Ca^{2+} chelator 1,2-bis (2-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid (BAPTA), which reduces the $[Ca^{2+}]_e$ to 0.3 μM, QA only elicits a transient intracellular Ca^{2+} rise of 16 nM, which is no longer measurable after a 5-min delay. This indicates that the major long-lasting $[Ca^{2+}]_i$ increase is due to a Ca^{2+} influx from the extracellular medium (TABLE 1).

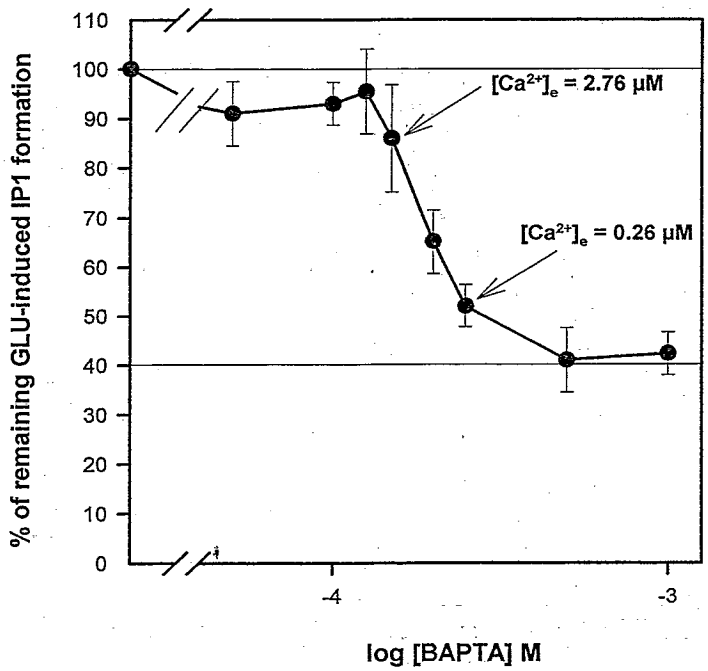

FIGURE 3. Effect of increasing concentrations of the Ca^{2+} chelator (BAPTA) on the IP1 formation elicited by Glu (1 mM). The IP1 formation elicited by Glu in the presence of 150 μM extracellular Ca^{2+} was taken as 100%. The values are the mean ± SD of three to four separate experiments. The method was previously described.[18] Briefly, 8-day-old rat forebrain synaptoneurosomes, preloaded with [^{3}H]-myo-inositol for 1 h at 37 °C (about 1 mg protein/mL) were incubated at 37 °C for 13 min in the presence of Li^+ (10 mM). The stimulation by QA lasts for a further 20 min, then the inositol phosphates (IPs) were extracted and separated by ion-exchange chromatography, and the radioactivity contained in the IP1 eluate was counted.

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TABLE 1. Intracellular Ca^{2+} Concentration Variations Elicited by Quisqualate in the Presence of Different Extracellular Ca^{2+} Concentrations

mGluR Agonist	$\Delta[Ca^{2+}]_i$ (nM) (1 min after QA application)	$\Delta[Ca^{2+}]_i$ (nM) (5 min after QA application)	$[Ca^{2+}]_e$ (μM)
QA (10 μM)	65 ± 7	71 ± 6	150
QA (10 μM)	16 ± 5	0 ± 2	0.3

Ca^{2+} INFLUX AND ITS CHARACTERISTICS

It has been extensively demonstrated that an influx of Ca^{2+}, either due to the action of depolarizing agents or to Ca^{2+} ionophores, stimulates the IP production.[42–47] Using increasing concentrations of BAPTA to reduce the $[Ca^{2+}]_e$, we found that about 60% of the Glu-induced inositol monophosphate (IP1) accumulation is due to the Ca^{2+} influx from the extracellular medium (FIG. 3). The remaining response (40%) corresponds to the direct IP1 accumulation solely resulting from the mGluR activation.

The VDCC antagonists, including verapamil, nifedipine, ω-conotoxin, flunarizine, ω-agatoxin IVA, and SC 38249 (a gift of Prof. J. Meldolesi) neither affect the Ca^{2+} influx nor the EAA-elicited IP production. This clearly indicates that the voltage-dependent N, L, T, and P type channels are not involved in these two effects.

At 100 μM, Zn^{2+}, Ni^{2+}, Co^{2+}, Ba^{2+}, and La^{3+} are without effect on the Glu-induced IP metabolism, whereas Mn^{2+} only slightly affects this response. Cd^{2+} and Hg^{2+} totally inhibit the Glu-elicited IP response.[47,48] However, this effect does not appear to be due to competitive blockade of the Ca^{2+} channel by these two ions. Cd^{2+} and Hg^{2+} most probably bind to free -SH groups of proteins involved in the transduction system.[48]

Mn^{2+}, which usually crosses the plasma membrane by the same pathways as Ca^{2+}—in particular by the VDCC—and quenches the Ca^{2+}-Fura-2 fluorescences,[49] is often used as a surrogate ion to monitor Ca^{2+} entry. However, in synaptoneurosomes, Mn^{2+} does not decrease the Ca^{2+}-Fura-2 fluorescence stimulated by QA. This further reinforces the conclusion that the Ca^{2+} influx does not occur via a classical VDCC.

Using stopped flow spectrofluorimetry, we demonstrated that the Ca^{2+} influx triggered by QA (10 μM) is delayed by about 300 ms as compared to that elicited by K^+ (30 mM) ions or the Ca^{2+} ionophore A23187 (2 μM).[41] This specific kinetic likely indicates that the Ca^{2+} influx is not directly mediated by the metabotropic receptor associated with a Ca^{2+} channel via a G-protein (GOC). Rather this delayed influx suggests the involvement of a multistep mechanism in which IP3 participates. It has previously been reported that IP3 synthesis requires about 150 ms after odorant stimulation of the olfactory cilia[50] and about 200 ms after thrombin stimulation of the human platelets.[51]

It does not appear that CRAC channels are involved in this response because La^{3+} ions, known to inhibit the current carried through CRAC channels, have no effect on the IP formation elicited by mGluR agonists[47] (TABLE 2).

Quinine and quinidine, able to inhibit CAN channels,[52] block in a dose-dependent manner the QA-elicited IP formation (data not shown). This result suggests the involvement of such CAN channels in the calcium entry, which follows

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TABLE 2. Comparison of Ca^{2+} Permeable Channels[a]

Channel	Trigger Direct or Indirect	Conductance	Permeation	Inhibitors
CRAC	EGTA BAPTA IP3 Ionomycin Thapsigargin	20 fS	$Ca^{2+} > Ba^{2+}, Sr^{2+} > Mn^{2+}$	Cd^{2+} La^{3+} Imidazole derivatives Cytochrome P450 Inhibitors (econazole)
SMOC	Ca^{2+} IP3 IP4	2–25 pS	$Ba^{2+} \sim Ca^{2+} \sim Mn^{2+}$	?
CAN	IP3 Thapsigargin Ca^{2+}	10–50 pS	Ca^{2+}, Na^+, K^+	Quinine Quinidine Replacement of Na^+ for NMDG

[a]CRAC, Ca^{2+} release-activated Ca^{2+} channel; SMOC, second messenger-operated Ca^{2+} channel; CAN, Ca^{2+}-activated nonspecific cation channel.

EAA metabotropic receptor activation. Moreover, substitution of Na^+ ions for *N*-methyl-D-glucamine, which also blocks this type of channel, inhibits the QA-evoked IP response.[46]

FACTORS THAT TRIGGER THE Ca^{2+} INFLUX

Taking into account the results from the rapid kinetics of the Ca^{2+} influx, one could accept that the synthesis of IP3 is required to trigger the Ca^{2+} influx. The next question then is, does IP3 activate the Ca^{2+} influx directly or indirectly, via the released Ca^{2+} from the endoplasmic reticulum pool, via the IP4 synthesis, or via the release of a diffusible factor such as CIF?[35] To answer this question, we by-passed the whole transduction system associated with the EAA metabotropic receptor and the synthesis of IP3. This was performed thanks to thapsigargin, which blocks the Ca^{2+} ATPase responsible for pumping the cytosolic Ca^{2+} into the endoplasmic reticulum.[52,53] This leads to an increase in intracellular Ca^{2+}, independent of the IP3 synthesis. Thapsigargin produces a strong depolarization accompanied by a Ca^{2+} influx in synaptoneurosomes. The chronology of these two events has been elucidated by showing that (1) thapsigargin still depolarizes the synaptoneurosomal membrane when Ca^{2+} influx is eliminated by reducing free extracellular Ca^{2+} with the chelating agent BAPTA; and (2) an intracellular Ca^{2+} chelator, BAPTA-AM (1,2-bis(2-aminophenoxy)ethane-*N*,*N*,*N'*,*N'*-tetraacetic acetoxymethylester), strongly decreases the thapsigargin-induced depolarization and the Ca^{2+} influx. Assuming that the first step of action of thapsigargin is to increase intracellular Ca^{2+} by blocking the Ca^{2+}-ATPase, one can deduce that the second event is the intracellular Ca^{2+}-induced depolarization, and finally the influx of Ca^{2+} from the extracellular medium. In addition, a strong correlation exists between the IP1 formation elicited by increasing concentration of thapsigargin and the $[Ca^{2+}]_i$ increase (FIG. 4). The correlation also holds true between thapsigargin-induced membrane depolarization and Ca^{2+} increase, as simultaneously measured using two fluorescent dyes, $DiSC_2(5)$ and Fura-2, respectively (FIG. 5). One could deduce that a high linkage exists

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between these three phenomena: IP3 synthesis, membrane depolarization, and intracellular Ca^{2+} increase.

DO EAA AND THAPSIGARGIN TRIGGER THE SAME MECHANISMS FROM THE FIRST INTRACELLULAR Ca^{2+} INCREASE?

From the above assumption, one could expect that thapsigargin and QA have no cumulative effects on the IP formation. Moreover, considering that only 60% of the IP1 formation induced by QA is dependent on the Ca^{2+} influx as previously demonstrated, one also could expect that QA-induced IP accumulation is larger than thapsigargin-elicited IP accumulation; these two assumptions are confirmed by experiments.[41] In addition, thapsigargin and QA both produce a Ca^{2+} entry, which is impermeable to Mn^{2+}. The hypothesis that EAA and thapsigargin activate the same mechanism is further reinforced by the fact that IP3 and thapsigargin are supposed to affect the same intracellular Ca^{2+} stores.[54,55] Finally, the Glu-elicited IP response

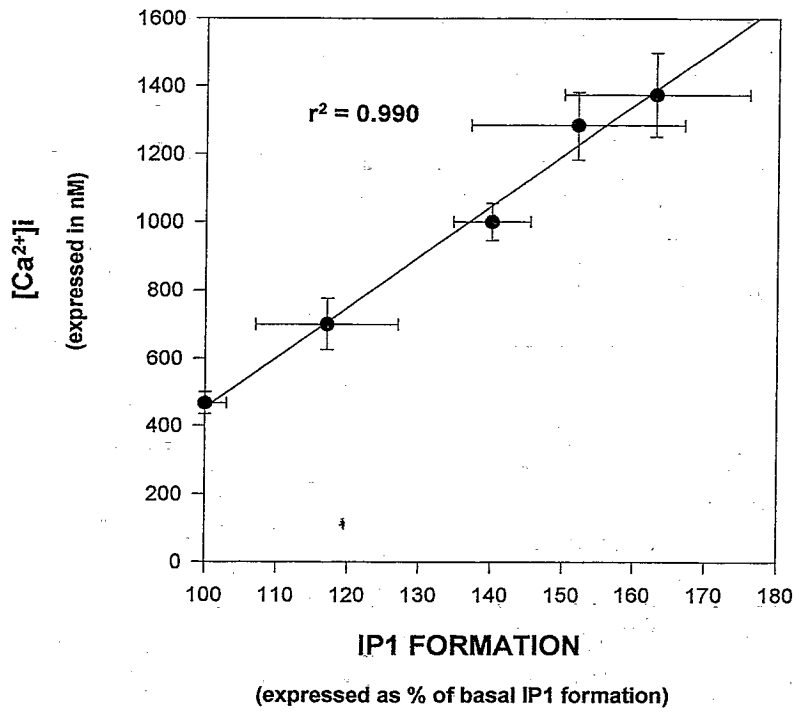

FIGURE 4. Dose-dependent effects of thapsigargin: Correlation between the intracellular Ca^{2+} increase and the IP1 formation produced by increasing concentrations of thapsigargin in 8-day-old rat forebrain synaptoneurosomes. Thapsigargin was tested at concentrations ranging from 0.1 to 10 μM. Each value is the mean ± SD of four separate experiments. Experiments were as previously described.[18,48]

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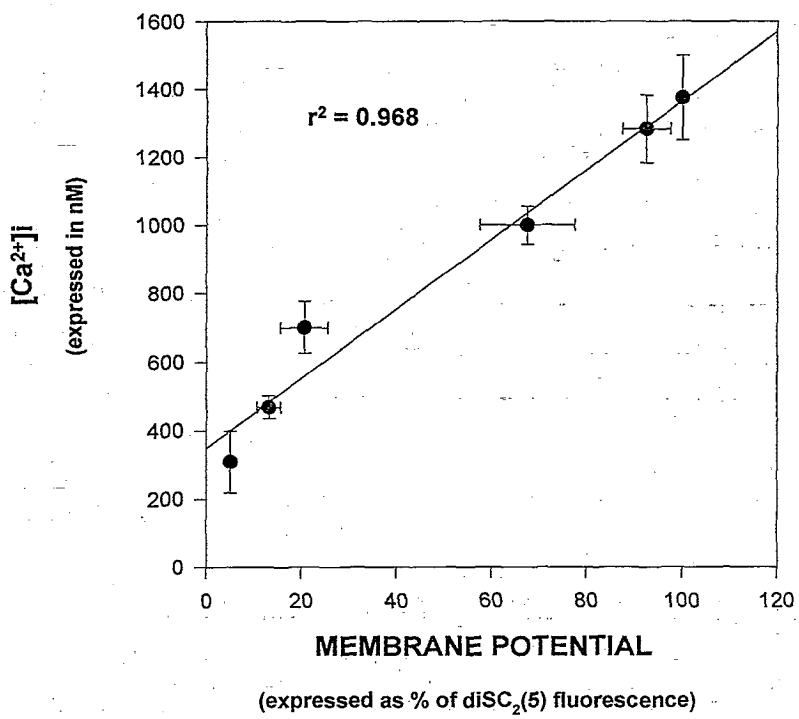

FIGURE 5. Dose-dependent effects of thapsigargin: Correlation between the intracellular Ca^{2+} increase and the membrane potential produced by increasing concentrations of thapsigargin in 8-day-old rat forebrain synaptoneurosomes as simultaneously measured using two fluorescent probes, Fura-2 for Ca^{2+} and $DiSC_2(5)$ for membrane potential. Thapsigargin was tested at concentrations ranging from 0.1 to 10 μM. Each value is the mean ± SD of four separate experiments. Methods were as previously described.[41,48]

is also partially blocked by BAPTA-AM. One could then suppose that thapsigargin and EAA stimulate the same mechanism and that Ca^{2+} is directly implicated in triggering Ca^{2+} influx from the extracellular medium rather than a releasable substance like CIF.

Because most neurotransmitter receptors linked to the phosphoinositide metabolism produces IP3 synthesis, one could speculate that $[Ca^{2+}]_i$-induced depolarization and a subsequent Ca^{2+} influx is a general phenomenon. However, the specificity of such a mechanism may arise from the fact that there is a concomitant association of the neurotransmitter receptor with the IP3-thapsigargin sensitive store, a $[Ca^{2+}]_i$-sensitive ionic channel producing the depolarization, an adequate voltage-dependent Ca^{2+} channel, sensitive to this depolarization, and the presence of Ca^{2+}-sensitive PLC. It appears that such an association is not always found, because in our experimental model, a muscarinic agonist, carbachol, does not at all trigger the same mechanism.[41,46–48]

In conclusion, we found that the stimulation of mGluR by glutamate, or related agonists, produces a self-maintained increase in $[Ca^{2+}]_i$ (see FIG. 6) via a first

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stimulation of IP3 formation, which in turn release Ca^{2+} from intracellular stores. The subsequent modest increase in $[Ca^{2+}]_i$ is sufficient to activate a $[Ca^{2+}]_i$-dependent ionic channels, which produces a depolarization. This depolarization opens a nonclassical voltage-dependent Ca^{2+} channel and allows a massive Ca^{2+} influx from the extracellular medium. The subsequent additional $[Ca^{2+}]_i$ increase activates Ca^{2+}-sensitive PLC, likely but not necessarily different from that directly linked to the mGluR. This induces a further IP3 production and the above cycle could begin again.

Many mechanisms could be involved in stopping this cycle, for example, a $[Ca^{2+}]_i$ threshold for activating the Na^+/Ca^{2+} exchanger to inhibit the IP3 receptor or the $[Ca^{2+}]_i$-dependent ionic channel, the exhaustion of the intracellular Ca^{2+} pool or the membrane phosphoinositide precursor pool. Nevertheless, we noticed a transient enhanced activity of this transduction mechanism, which appears to be specific for the glutamatergic system, at a period of development when synaptic contact is being formed.[56,57] Consequently, this mechanism may play a key role, when high $[Ca^{2+}]_i$ is required for inducing cytoskeletal rearrangement and gene expression likely necessary for shaping and maintaining the newly formed synaptic contacts.

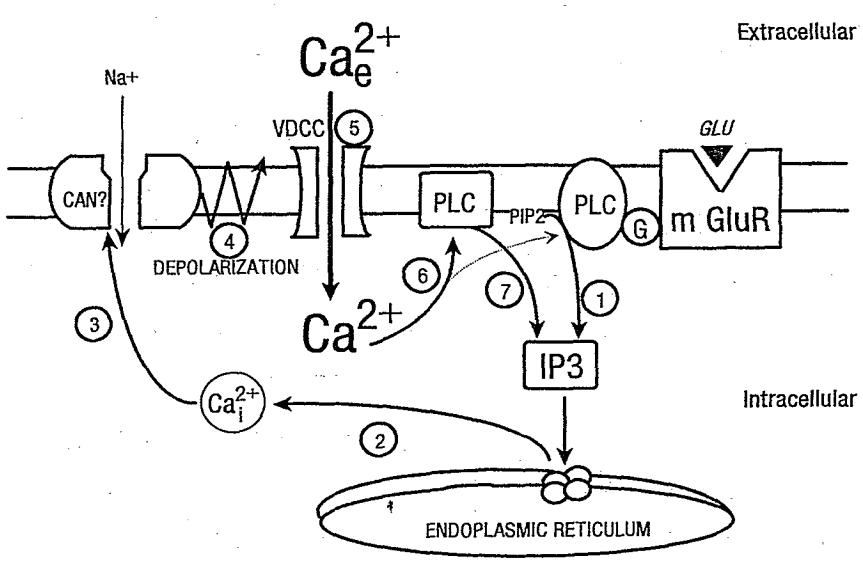

FIGURE 6. Putative mechanism triggered by the activation of metabotropic glutamate receptors (mGluR). (1) Synthesis of inositol-1,4,5-trisphosphate (IP3) from the membrane precursor inositol phospholipid: phosphatidyinositol-4,5-bisphosphate (PIP2). (2) Release of Ca^{2+} from the endoplasmic reticulum following IP3 interaction with its receptor. (3) Activation by intracellular Ca^{2+} of an ion channel, likely a Ca^{2+}-activated nonspecific cation channel (CAN). (4) Activation of CAN produces a local depolarization, which (5) opens a nonclassical voltage-dependent Ca^{2+} channel (VDCC). (6) The massive Ca^{2+} influx originating from the extracellular medium activates Ca^{2+}-sensitive phospholipase C (PLC), and possibly the PLC linked to the mGluR. (7) Activation of the Ca^{2+}-dependent PLC further increases the IP3 formation. This proposed mechanism leads to a self-sustained or even self-amplified intracellular Ca^{2+} concentration increase.

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